Complete Summary

GUIDELINE TITLE

The Society of Thoracic Surgeons practice guideline series: aspirin and other anti-platelet agents during operative coronary revascularization.

BIBLIOGRAPHIC SOURCE(S)

Society of Thoracic Surgeons (STS). The Society of Thoracic Surgeons practice guideline series: aspirin and other anti-platelet agents during operative coronary revascularization. Chicago (IL): Society of Thoracic Surgeons (STS); 2003. 38 p. [190 references]

GUIDELINE STATUS

This is the current release of the guideline.

** REGULATORY ALERT **

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

On February 8, 2006, the U.S. Food and Drug Administration (FDA) issued a public health advisory and other advisory information to notify both healthcare professionals and consumers of recently published studies of serious renal and cardiovascular toxicity following Trasylol (aprotinin) administration to patients undergoing coronary artery bypass grafting surgery (CABG). An observational study published in The New England Journal of Medicine reported that Trasylol may be associated with increased risk of myocardial infarction, stroke and renal dysfunction. Another publication (Transfusion, on-line edition, January 20, 2006) has reported that Trasylol administration may increase the risk for renal toxicity.

The FDA is working with the authors of the publications and the manufacturer of Trasylol to carefully evaluate the risks and benefits associated with use of Trasylol in CABG. The FDA anticipates the public presentation of the recently reported information and other data at an advisory committee in the near future. The FDA will notify health care providers and patients in a timely fashion as new information becomes available. See the FDA Web site for more information.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Conditions requiring operative coronary revascularization

GUIDELINE CATEGORY

Management

CLINICAL SPECIALTY

Cardiology
Emergency Medicine
Thoracic Surgery

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

- To assist physicians and other health care providers in clinical decision-making by describing a range of generally acceptable approaches for the diagnosis, management, or prevention of specific diseases or conditions
- To provide specific recommendations for managing anti-platelet medications, especially aspirin, in patients who require operative intervention

TARGET POPULATION

Patients requiring urgent/emergent or elective operative coronary revascularization

INTERVENTIONS AND PRACTICES CONSIDERED

1. Aspirin
2. Heparin
3. Low-molecular-weight heparins

4. Warfarin
5. Direct thrombin inhibitors
6. Adenosine diphosphate (ADP) receptor blockers
7. Glycoprotein IIb/IIIa inhibitors
8. Blood sparing methods (hemostatic drug therapy [aprotinin], lysine analogues, and other blood conservation methods [e.g., peripheral blood sparing devices, permissive perioperative anemia])

MAJOR OUTCOMES CONSIDERED

Benefits, risks, efficacy and safety of aspirin and other anti-platelet agent use in the perioperative setting for coronary revascularization

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The guideline development panel searched several sources for available evidence about specific questions relating to the use of aspirin before, during and after cardiac operations.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Level of Evidence

Level A: Data from well-designed placebo-controlled, blinded, randomized clinical trials or meta-analyses

Level B: Data from less well done single randomized trials or from nonrandomized, analytical observational studies.

Level C: Consensus 'expert' opinion or data from descriptive studies or informative case reports

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

In developing these guidelines, the guideline developers reviewed the available evidence and arrived at consensus recommendations.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Classification of Recommendations

Class I: Evidence or general agreement that given procedure or intervention is useful or effective.

Class II: Conflicting evidence exists about the usefulness of an intervention or procedure.

- II.a.: Weight of evidence favors intervention or procedure
- II.b.: Usefulness of intervention or procedure is less well established

Class III: Evidence exists that intervention/procedure is not useful and/or is possibly harmful

COST ANALYSIS

Guideline developers reviewed studies (including meta-analyses, randomized trials and observational studies) to suggest that aspirin is an extremely cost-effective and efficacious drug for the secondary prevention of myocardial events among patients with stable and unstable coronary artery disease.

METHOD OF GUIDELINE VALIDATION

Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Not stated

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

The levels of evidence (A-C) and classification of recommendations (I-III) are defined at the end of the "Major Recommendations" field.

Beneficial Effects of Aspirin in the Perioperative Setting

Does preoperative aspirin improve outcomes after Coronary Artery Bypass Graft (CABG)?

Effect on Graft Patency

Multiple CABG studies show that aspirin reduces the frequency of saphenous vein graft occlusion compared to placebo, whether given 1 day before operation, on the day of operation or on the day after operation. No similar benefit is conferred when only internal thoracic artery grafting is used for CABG. Effective doses of aspirin that improve saphenous vein graft patency range from 100 to 975 mg per day. The majority of available Level A studies evaluating the effect of aspirin on graft patency suggest that 325 mg/day is the optimal dose for improving graft patency but both lower and higher doses may have equal efficacy. Dipyridamole therapy added to aspirin does not confer a significant additional benefit on graft patency compared to aspirin alone. Aspirin provides protection from cardiovascular events in patients with known atherosclerotic heart disease, especially CABG patients. For this reason, aspirin therapy should be continued beyond one year unless side-effects limit therapy. In summary, available evidence suggests that aspirin (325 mg/day) should be given for at least one year after operation in order to improve the patency of saphenous vein grafts (Class I recommendation).

Effect on Event Reduction in Patients with Known CAD

Aspirin decreases short-term mortality after myocardial infarction and in patients with unstable coronary syndromes. Furthermore, aspirin also decreases long-term all-cause mortality in patients with known or suspected coronary disease. There are multiple Level A and B studies (including meta-analyses, randomized trials and observational studies) to suggest that aspirin is an extremely cost-effective and efficacious drug for the secondary prevention of myocardial events among patients with stable and unstable coronary artery disease. Direct and indirect comparisons of high-risk patients suggest no statistical differences in efficacy and hemorrhagic strokes across aspirin dosages. These comparisons, however, suggest decreased risk of gastrointestinal symptoms with lower doses of aspirin. In fact, available evidence suggests that aspirin improves all-cause mortality and, unless contraindicated, should be given to patients with known coronary artery disease (CAD) (Class I recommendation).

In patients with known coronary disease who are having CABG, to deny aspirin for a prolonged period of time would be ill-advised. There are limited data available regarding the discontinuation of aspirin for short periods of time in either the elective or urgent/emergent pre-CABG situation (see recommendations below).

Harmful Effects of Aspirin in the Perioperative Setting

Does Preoperative Aspirin Cause Increased Postoperative Blood Loss?

Much has been written about the effects of preoperative aspirin on postoperative bleeding and blood transfusion. Table 2 in the original guideline document summarizes the available evidence reviewing the effect of preoperative aspirin on postoperative bleeding. Of the 21 studies identified, there were 6 randomized controlled trials (RCTs) that were viewed as Level A evidence. All RCTs, except one, found that preoperative aspirin results in either increased blood loss as measured by drainage from mediastinal tubes, increased transfusion rates, or increased frequency of re-exploration. Multiple other articles with level B or C quality evidence have less clear cut association of preoperative aspirin with increased blood loss after cardiac procedures (Table 2). Because of the consistent finding of aspirin-associated increased blood loss in the highest quality studies, the guideline development panel feels that patients who receive aspirin before operation are at increased risk for above normal postoperative bleeding and blood transfusion after operation. There is a longitudinal trend to the risk of aspirin-induced postoperative bleeding with studies done earlier than 1994 being more likely to show aspirin-related postoperative bleeding and later studies less likely to show aspirin-related postoperative bleeding. It is likely that improvements in blood conservation, cardiopulmonary bypass techniques and other technical advances may lessen the risk of bleeding in aspirin treated patients in the current era, but no certain explanation of this longitudinal trend is available.

It is possible to estimate the amount of increased bleeding associated with preoperative aspirin usage. In the randomized trials of CABG patients, preoperative aspirin results in between 200 and 400 cc of increased chest tube drainage and between 0.5 and 1 unit of increased packed red blood cell transfusion compared to controls. At least one study suggests that smaller doses of preoperative aspirin (81 mg) have a beneficial effect on graft patency with less risk of postoperative bleeding. Likewise, there is evidence from the cardiology literature that lower doses of aspirin are associated with a greater reduction in the vascular events than are higher doses (19% reduction with daily dose of 500-1500 mg compared to 32% reduction in patients taking 75-150 mg daily). This suggests that lower doses of preoperative aspirin provide equal or better protection for prevention of vascular events while minimizing postoperative bleeding. The explanation for this may be related to the ability of lower doses of aspirin to inhibit platelet thromboxane production without significant impact on vascular prostacyclin synthesis, but other mechanisms are possible.

A single nonrandomized study evaluated the risk of bleeding in patients having off-pump coronary artery bypass (OPCAB). In 340 patients having OPCAB, there was no difference in blood loss between aspirin users and non-users. Coronary revascularization without the use of cardiopulmonary bypass may limit aspirin-related postoperative bleeding.

To summarize, there is mostly Level A evidence (somewhat distorted by conflicting Level B evidence) that aspirin causes increased bleeding after CABG. The amount of aspirin-induced increased bleeding is small, is possibly dose related, and may be minimized with good perioperative blood conservation or by using off-pump procedures.

Should aspirin be stopped before operation?

Aspirin is one of the essential treatments for patients with unstable angina or for patients who have had a recent myocardial infarction. Because of this treatment imperative, urgent/emergent patients require aspirin as part of their treatment regimen to reduce undesirable short- and long-term cardiovascular outcomes from coronary events some of which may require CABG. Patients on aspirin who present with an acute coronary syndrome have less severe clinical presentation, fewer hospital complications, and lower in-hospital death rates than patients not previously taking ASA. Similarly a single observational study suggests that taking aspirin before CABG reduces the operative risk compared to non-aspirin users. This suggests that patients who suffer perioperative ischemic events may benefit from preoperative aspirin therapy. The guideline development panel feels that perioperative ischemia is more likely in urgent/emergent CABG patients and that these same patients derive the most benefit from preoperative aspirin. Hence, for urgent/emergent coronary artery bypass graft (CABG) patients, the small risk of bleeding is outweighed by the benefits of aspirin. This leads to a Class IIa recommendation to continue aspirin until the time of CABG in urgent/emergent patients. This recommendation applies to patients having CABG who are not in one of the aspirin-sensitive high-risk subgroups listed in the Table below. A corollary of this recommendation is that unstable/emergent patients who are not on aspirin before operation should receive a dose of aspirin unless they fall into one of the aspirin-responsive high-risk categories listed in the Table below.

Aspirin inhibits platelet cyclooxygenase activity irreversibly. Whole body platelet function returns toward normal as new platelets are formed and released from the bone marrow. Bleeding time and platelet thromboxane B2 levels return to normal once approximately half the platelet pool is regenerated, 3-5 days after stopping the drug. Because of this, delay of elective operation and discontinuation of aspirin for a few days will allow the platelet effects of aspirin to dissipate. There is only anecdotal information available about the discontinuation of aspirin before elective CABG. The substrate in the coronary circulation in elective patients is not expected to be as threatening as in the urgent/emergent situation where active platelet aggregation is likely to be an important physiologic process. The results of cessation of aspirin therapy for short periods (i.e. a few days) are uncertain but logic would dictate that no major harmful clinical effects on long-term outcome occur in elective patients. For the totally elective CABG patient, without recent myocardial infarction or without an acute coronary syndrome (estimated to be no more than 20% of the CABG population based on the STS database) it is reasonable (expert opinion - Level C evidence) to stop aspirin 3-5 days before elective operation. Based on expert opinion, on randomized trials and on multiple, somewhat divergent observational studies of aspirin-induced postoperative bleeding (see Table 2 in the original guideline document), there is a Class IIa recommendation to stop aspirin for 3-5 days before elective CABG operations in order to reduce transfusion-related complications. There is a Class I recommendation to start aspirin in the early postoperative period after operation to improve bypass graft patency and all-cause mortality related to coronary artery disease in totally elective CABG patients. The guideline development panel recognizes that there is almost no evidence to document the effect on long-term cardiovascular end-points of discontinuing aspirin for a few days in this setting but

feels that the risk is small and is outweighed by the benefit from reduced blood transfusion in non-aspirin users.

Table: Aspirin Interaction with High Risk Drugs or Disease States

Preoperative Drug or Disease State	Effect in CABG Patients	Interaction with Aspirin	Level of Evidence	Recommendation in Preoperative CABG Patients
Heparin (UFH)	No discernible effect on postoperative bleeding if stopped shortly before skin incision	Most urgent/emergent patients given heparin are also on aspirin. No known interaction with aspirin.	B	Continue heparin until 1-2 hours before CABG (Class I)
Low Molecular Weight Heparin (LMWH)	Increased bleeding, blood transfusion, and re-exploration within 12-24 hours of dose. Effects gone within 24 hours	Almost all patients studied were taking aspirin for unstable coronary syndromes or recent myocardial infarction (MI). No known interaction with aspirin.	B	Stop LMWH 18-24 hours before operation - replace with unfractionated heparin 12 hours before operation. (Class IIa)
Warfarin	Routinely stopped several days before operation with conversion to unfractionated heparin until operation. No increased bleeding risk at operation. Warfarin restarted 1-2 days after operation. Addition of postoperative aspirin to Warfarin does not provide clear benefit but increases bleeding risk.	Aspirin combined with Warfarin almost always results in increased bleeding events but questionable benefit in secondary prevention.	B	Aspirin is not indicated in patients who require Warfarin therapy after CABG unless exceptional thrombotic risk exists (Class III)
Direct thrombin inhibitors (e.g., hirudin, bivalirudin, etc.)	No information available on the preoperative administration of these agents. Unlikely to be a problem in the	Unknown	C	Continue short acting agents up until immediately before CABG if appropriate indication. Longer acting agents should be replaced with

Preoperative Drug or Disease State	Effect in CABG Patients	Interaction with Aspirin	Level of Evidence	Recommendation in Preoperative CABG Patients
	case of short acting agents (e.g. bivalirudin). Longer acting agents (hirudin & argatroban) are associated with increased bleeding.			unfractionated heparin before CABG (Class IIb).
Platelet ADP receptor blockers (e.g., ticlopidine & clopidogrel)	Significant increased bleeding and blood transfusion in the presence or absence of aspirin.	Aspirin worsens the platelet defect induced by ADP receptor blockers	A	Stop ADP receptor blocker for 5-7 days before CABG (Class I -- also the recommendation of ACC/AHA)
Platelet glycoprotein IIb/IIIa inhibitors (e.g., abciximab, tirofiban, aggrastat)	Increased blood loss if administered within 12-24 hours of operation with long acting agents. Experience with short acting agents is mixed, but most studies suggest stopping with 4-6 hours of operation.	Aspirin worsens the platelet defect induced by GPIIb/IIIa receptor blockers.	B	Discontinue GP IIb/IIIa inhibitors before operation. Timing varies with agent used. (Class IIb).

Are There High-risk Patients Who Are Made Worse by Giving Aspirin Before Operation?

Various drugs and disease states are reported to influence bleeding during and after CABG. In some cases preoperative aspirin may interact with these conditions. The above table is a partial list of some of these agents or diseases. There are no well-controlled studies to guide treatment in most of the high risk situations described in the above table, but in each case an expert consensus based on available evidence was sought in order to provide recommendations.

Heparin

There is a substantial body of evidence to suggest that unfractionated heparin (UFH), when added to aspirin, is of benefit in patients with acute coronary syndromes (ACS) or with recent myocardial infarction (MI).There is no evidence to suggest that UFH, continued to within a few hours of CABG, increases postoperative blood loss, either in the presence or absence of preoperative aspirin (see above or Table 5 in the original guideline document). Unfractionated

heparin should be continued up until a short time before the skin incision in CABG patients who have an appropriate indication for heparin (Class I).

Low-Molecular-Weight Heparins (LMWH)

Some low molecular weight heparins (LMWH) improve outcomes, compared to UFH, after acute coronary syndromes. Inevitably, some patients with ACS or recent MI will need CABG. In this setting, almost all patients will also have been given aspirin as part of the standard treatment of ACS. Some studies suggest a small benefit of LMWH compared to unfractionated heparin, but this remains to be validated. A preponderance of studies suggests that LMWH, when given within 12-24 hours of CABG, results in increased bleeding after operation (see above or Table 5 in the original guideline document). Since LMWH has a 4-5 hour half-life, almost all of the dose is gone after 24 hours (5 half-lives). One study has suggested that the bleeding risk may not go away for at least 24 and possibly 48 hours. This leads to a Class IIa recommendation to stop low-molecular-weight heparin 18-24 hours before operation and replace it with unfractionated heparin if anti-thrombin therapy is indicated.

Warfarin

In patients with indications for long-term anticoagulation, warfarin is routinely stopped several days before major operative procedures to allow the INR to return to a normal or near-normal value. In patients at high risk of thromboembolism such as patients with atrial fibrillation and a mechanical valve or patients with two mechanical valves, UFH or LMWH therapy is started preoperatively within 24 to 48 hours of discontinuing warfarin. As discussed above, UFH should be continued up until a short time before CABG, while the last dose of LMWH should be given 18-24 hours before skin incision and replaced with UFH twelve hours before surgery (see above or Table 5 in the original guideline document). In patients who will need long-term anticoagulation after CABG, warfarin is resumed on the first or second postoperative day and UFH or LMWH may be administered simultaneously, until a therapeutic INR has been achieved.

In these patients there is little data available to address the question of whether aspirin, when added to warfarin post CABG is effective for secondary prevention. Conflicting data have been obtained from randomized trials. Several randomized trials including a meta-analysis of over 20,000 patients with coronary artery disease show a greater cardiovascular risk reduction with moderate to high intensity warfarin alone or in combination with aspirin compared to aspirin alone. However, both the Coumadin Aspirin Reinfarction Study (CARS) and the Combination Hemotherapy and Mortality Prevention (CHAMP) study found no benefit of low intensity warfarin therapy combined with aspirin compared to aspirin alone. However, in patients with an absolute indication for warfarin therapy, none of these studies answers the question of whether aspirin plus warfarin is superior to warfarin alone post CABG.

A double blind, randomized trial compared aspirin plus placebo and warfarin plus placebo to warfarin plus aspirin in 135 patients with prior CABG and acute coronary syndromes who were poor candidates for revascularization and found no significant difference in the primary endpoint of death, myocardial infarction or

unstable angina at one year follow up. In the Warfarin, Aspirin, Reinfarction Study (WARIS II), it was found that the combination of aspirin and warfarin resulted in a significant risk reduction compared to aspirin plus placebo but no reduction in risk compared to the warfarin alone in patients hospitalized for acute myocardial infarction. Taken together, the available data do not provide evidence that aspirin will add significantly to the secondary prevention provided by warfarin alone, but will likely increase the bleeding risk. Aspirin is not indicated in post CABG patients who are on long-term anticoagulant therapy with warfarin unless exceptional thrombotic risk is identified (Class III recommendation, level of evidence B).

Direct Thrombin Inhibitors

Direct thrombin inhibitors are used to improve outcomes following ischemic coronary events and during percutaneous interventions. Because of the short acting nature of some of these agents (e.g. bivalirudin), they are unlikely to cause significant bleeding during CABG, although there is no published information on the preoperative administration of these agents before CABG. Some of the direct thrombin inhibitors are used as heparin substitutes during on-pump and off-pump CABG, especially in patients with heparin induced thrombocytopenia. If short acting direct thrombin inhibitors are indicated (e.g. bivalirudin), there is no need to stop them until immediately before operation (Class IIa recommendation). Other longer acting direct thrombin inhibitors should be stopped and replaced with unfractionated heparin at an appropriate time before CABG consistent with the biologic half-life of the thrombin inhibitor.

Adenosine Diphosphate (ADP) Receptor Blockers

Agents that block the platelet ADP receptor provide important benefit to patients having coronary stent implantation, especially in patients with prior CABG. When clopidogrel is added to aspirin for the treatment of ACS, there is significant incremental benefit but also increased bleeding risk. ADP-receptor blocking agents should be used in patients with coronary artery disease who require aspirin but can not take the drug because of sensitivity or gastrointestinal bleeding. These factors and others result in many patients presenting for CABG who have taken clopidogrel, the most commonly used ADP receptor blocker. Multiple observational studies document the increased bleeding associated with the preoperative use of clopidogrel but no large randomized clinical trial has been performed (see above or Table 5 in the original guideline document). Because of the risk of excessive postoperative bleeding, ADP receptor blockers should be stopped 5-7 days before CABG (Class I recommendation -- also recommendation of American College of Cardiology (ACC)/American Heart Association (AHA).

Glycoprotein IIb/IIIa inhibitors

Clinically available short-acting and long-acting inhibitors of the platelet glycoprotein IIb/IIIa (GP IIb/IIIa) receptor for fibrinogen cause profound platelet dysfunction. There are three GP IIb/IIIa receptor antagonists currently available for clinical use -- two short-acting (eptifibatide and tirofiban) and one long-acting (abciximab). The current ACC/AHA guidelines for unstable angina indicate that GP IIb/IIIa inhibitors should be administered to patients having early catheterization and planned percutaneous intervention (Class I recommendation) and to patients

with ongoing ischemia or other high risk features (Class IIa recommendation). Patients on GP IIb/IIIa receptor antagonists who require emergency surgical revascularization may be at increased risk for excessive postoperative bleeding, particularly with abciximab but less so with the shorter acting agents. Operation can be performed shortly after cessation of the short acting agents, but within 12-24 hours for abciximab. Platelet transfusion has been shown to successfully reduce the incidence of post-CABG bleeding complications in patients taking GPIIb/IIIa receptor antagonists before operation. Because of the bleeding risk, these agents should be discontinued before CABG (Class IIb recommendation). The recommended time from stopping GP IIb/IIIa inhibitors until operation varies depending on the agent used but ranges from four to six hours for the short acting agents to 12-24 hours for abciximab. No Level A or B evidence supports exact timing of discontinuation of these agents; hence, only rough estimates are available. Some authors suggest, based on observational data, that short-acting GP IIb/IIa receptor antagonists can be continued up until operation, but given the conflicting conclusions in the literature, safe practices would suggest that stopping short acting agents before operation is preferred in order to minimize blood loss and blood transfusion.

Aspirin Resistance & Hyper-responders

Five to 10% of patients who take aspirin do not have a complete anti-platelet effect from the usual doses prescribed, and the effect of a dose of aspirin may vary over time. These patients have more than a threefold increase in cardiovascular events when followed for a prolonged period of time. This incidence of aspirin resistance may be higher in patients undergoing CABG, and may be related to a variety of gene polymorphisms. Higher doses of aspirin may ameliorate this aspirin resistance. Incidentally, there is likely to be variability in the therapeutic effect for ADP-receptor blockers also, similar to that seen with aspirin. In patients with resistance to the usual doses of anti-platelet drugs, increased doses and the addition of other anti-platelet drugs are the accepted method of obtaining a suitable anti-platelet response.

There is evidence that certain patients have an accentuated response to the usual doses of preoperative aspirin. Certain 'hyper-responders' to average doses of aspirin exhibit very prolonged skin bleeding times. This accentuated response to aspirin may result in increased perioperative blood loss worsened by preoperative aspirin therapy. The mechanisms of these effects of aspirin are undoubtedly multifactorial and include the anti-platelet, anti-inflammatory, anticoagulant and endothelial-protecting actions of aspirin (see Table 1 in the original guideline document).

Thrombocytopenia - Idiopathic Thrombocytopenic Purpura (ITP), Heparin-Induced Thrombocytopenia without/with Thrombosis (HIT/HITT), Myelodysplastic Syndrome, etc.

Patients with thrombocytopenia from whatever cause (defined as platelet count below 50,000) are at extremely high risk of excessive bleeding after CABG (see above or Table 5 in the original guideline document). Aspirin is harmful in these patients and should not be administered (Class III recommendation).

Qualitative Platelet Defects

Additionally, patients who have average blood loss during CABG, but who start out with low red blood cell volumes either from small body size or from preoperative anemia (e.g. renal failure, repeated blood drawing during prolonged intensive care unit (ICU) stay, multiple recent percutaneous procedures, etc.) exhibit increased perioperative blood transfusion that could be worsened by preoperative aspirin. One of the earliest observations about anemia was that bleeding time was prolonged in anemic patients. Anemia-related bleeding abnormalities are likely to be worsened by aspirin. Patients with other congenital or acquired qualitative platelet defects are at increased bleeding risk. Congenital defects include von Willebrand's disease, Bernard-Soulier syndrome, Glanzmann's thrombasthenia, storage-pool disease and others. Acquired qualitative defects are seen in liver disease, renal disease and drug induced qualitative platelet defects. Aspirin should be stopped in patients with a qualitative platelet defect, either related to anemia or to congenital or acquired platelet defects (Class IIa recommendation).

How Should High-Risk Patients Be Managed If Aspirin Cannot Be Stopped Before CABG?

It is inevitable that some high-risk patients defined above or in Table 5 in the original guideline document will have taken aspirin shortly before CABG. In some of these high-risk patients aspirin adds to the substantial risk of excessive blood transfusion but, for one reason or another, can not be discontinued before operation. There are multiple blood conservation interventions that should be used to reduce the risk in these aspirin-treated patients. Many authors emphasize the importance of a multifactorial approach to blood conservation. In the patient who falls into one of the aspirin-sensitive high risk groups listed above or in Table 5 in the original guideline document, evidence suggests that the optimal approach to blood conservation should employ a combination of several interventions including hemostatic drug therapy (aprotinin), peripheral blood sparing devices and permissive perioperative anemia. Perhaps the best documented of these interventions is the use of hemostatic drugs. At least eight randomized trials suggest that aprotinin limits blood loss and transfusion in patients given aspirin before CABG. Some residual concerns exist regarding the effect of aprotinin on graft patency. Although this is an area of controversy, emerging evidence suggests that aprotinin has limited effect on graft patency if adequate heparinization is used and other factors that influence graft patency are taken into consideration. Consensus suggests that there is level A and B evidence that aprotinin limits bleeding in aspirin-treated patients requiring CABG with a good safety profile. This leads to a Class IIa recommendation for the use of aprotinin in aspirin-treated CABG patients who fall into the high-risk categories listed above or in Table 5 in the original guideline document.

These recommendations cannot be extrapolated to substitute the lysine analogue antifibrinolytics (tranexamic acid or epsilon aminocaproic acid) for aprotinin. The evidence is not nearly as compelling for non-aprotinin antifibrinolytics. The guideline development panel recognized that many surgeons use lysine analogues for their anti-fibrinolytic effect in aspirin-treated patients who require CABG, despite lack of available evidence of their benefit in this group. While lysine analogues are not the best option to reduce postoperative bleeding in

high-risk aspirin-treated patients (see above or Table 5 in the original guideline document) who require CABG, many surgeons use them for this indication without harmful side-effects. Consensus suggests that these drugs can be used to limit postoperative bleeding, recognizing that they are not the best option. (Class IIb recommendation).

Perioperative blood sparing techniques, when combined with hemostatic drug therapy are likely to limit blood loss in the high-risk aspirin treated patient. These methods include salvage of blood from the heart-lung machine, blood pooling at the onset of cardiopulmonary bypass, and possibly the use of off-pump procedures.

Other blood conservation methods that have proven efficacy in elective CABG procedures are not likely to be helpful in the setting of urgent/emergent high risk aspirin sensitive patients and are not indicated. These methods include predonation of autologous blood, erythropoietin treatment and preoperative platelet-pheresis (Class III).

Definitions

Level of Evidence

Level A: Data from well-designed placebo-controlled, blinded, randomized clinical trials or meta-analyses

Level B: Data from less well done single randomized trials or from nonrandomized, analytical observational studies.

Level C: Consensus 'expert' opinion or data from descriptive studies or informative case reports

Classification of Recommendations

Class I: Evidence or general agreement that given procedure or intervention is useful or effective.

Class II: Conflicting evidence exists about the usefulness of an intervention or procedure.

- II.a. Weight of evidence favors intervention or procedure
- II.b. Usefulness of intervention or procedure is less well established

Class III: Evidence exists that intervention/procedure is not useful and/or is possibly harmful

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of evidence supporting the recommendations is specifically stated for each recommendation (see 'Major Recommendations' field).

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate and effective utilization of anti-platelet medications, especially aspirin, in patients who require operative intervention

POTENTIAL HARMS

- There is evidence that aspirin causes increased bleeding after coronary artery bypass graft (CABG).
- There is evidence that certain patients have an accentuated response to the usual doses of preoperative aspirin. Certain 'hyper-responders' to average doses of aspirin exhibit very prolonged skin bleeding times.

CONTRAINDICATIONS

CONTRAINDICATIONS

Aspirin is contraindicated in patients at high risk for excessive bleeding after coronary artery bypass graft, such as:

- Patients with thrombocytopenia
- Patients with qualitative platelet defects, either related to anemia or to congenital or acquired platelet defects
- Patients with aspirin resistance or hyper-responders

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- These guidelines should not be considered inclusive of all proper methods of care or exclusive of other methods of care reasonably directed at obtaining the same results. Moreover, these guidelines are subject to change over time, without notice. The ultimate judgment regarding the care of a particular patient must be made by the physician in light of the individual circumstances presented by the patient.
- Evidence-based guidelines are an attempt to reconcile often conflicting lines of evidence, giving greater weight to evidence derived from more methodologically rigorous studies and those for which the overall weight of evidence is most convincing. They must be viewed as guidelines and recommendations, not absolutes.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Society of Thoracic Surgeons (STS). The Society of Thoracic Surgeons practice guideline series: aspirin and other anti-platelet agents during operative coronary revascularization. Chicago (IL): Society of Thoracic Surgeons (STS); 2003. 38 p. [190 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2003

GUIDELINE DEVELOPER(S)

Society of Thoracic Surgeons - Medical Specialty Society

SOURCE(S) OF FUNDING

Society of Thoracic Surgeons

GUIDELINE COMMITTEE

Workforce on Evidence-Based Medicine

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Workforce Members: Victor A. Ferraris, M.D., Ph.D. (Aspirin Guideline Taskforce Chair); Suellen P. Ferraris, Ph.D.; David J. Moliterno, M.D.; Philip Camp, M.D.; Jeanine M. Walenga, Ph.D.; Harry L. Messmore, M.D.; Walter P. Jeske, Ph.D.; Fred H. Edwards, M.D; David Royston, M.D.; David M. Shahian, M.D.; Eric Peterson, M.D.; Charles R. Bridges, M.D., Sc.D.; George Despotis, M.D.

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the Society of Thoracic Surgeons Web site.

Print copies: Available from The Society of Thoracic Surgeons, 633 N. Saint Clair St., Suite 2320, Chicago, IL, USA 60611-3658

AVAILABILITY OF COMPANION DOCUMENTS

None available

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on March 25, 2005. The information was verified by the guideline developer on May 2, 2005. This summary was updated by ECRI on February 14, 2006 following the U.S. Food and Drug Administration (FDA) advisory on Trasylol (aprotinin).

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Date Modified: 9/25/2006